REMARKS

In general, applicants' invention features a novel gene family, the members of which encode regulators that control the onset of acquired resistance responses in plants. This invention is based on applicants' discovery of a gene encoding a novel disease resistance protein characterized by the presence of ankyrin repeats, as well as their finding that the transformation of the cloned gene into plants conferred broad-spectrum disease resistance. Importantly, the invention provides for the genetic engineering of long-lasting, broad-spectrum resistance in crops.

Office Action

Claims 1, 2, 4-13, 15-29, 36, and 40-42 were examined in this case. Claims 17-29, 36, and 40-42 were objected to for improper form. Claims 1, 2, 4-13, 15, and 16 were rejected under 35 U.S.C. § 112, first paragraph and § 102(e). Claims 1, 2, 4-13, 15, and 16 were also provisionally rejected for double patenting. Each of these rejections is addressed as follows.

Support for the Amendments

Claims 17, 22, 36, and 40 have been amended to incorporate the limitations of claims 1, 10-12, and 16. New claims 43-48 specify that the nucleic acid complements an acquired resistance mutant (see, for example, page 7, lines 8-10).

The specification has been amended to replace each hyperlink with a reference to the corresponding website that does not include browser-executable code. The title and abstract were also amended to more clearly recite the claimed invention as disclosed, for example, on pages 6-10.

A marked-up version indicating the amendments made to the specification and claims, as required by 37 C.F.R. § 1.121(b)(1)(iii) and (c)(1)(ii), and a list of pending claims are enclosed. These amendments add no new matter.

Objection to the Drawings and Specification

The Examiner states that corrected drawings are required. As applicants hereby enclose corrected drawings that comply with the guidelines listed on form PTO-948, this objection may now be withdrawn.

The Examiner also states that the specification is objected for containing embedded hyperlinks and for containing a title and abstract that are not descriptive of the claimed invention. In response to these objections, applicants have amended the specification to eliminate all hyperlinks and have amended the title and abstract to more clearly describe the claimed invention. Accordingly, these objections may now be withdrawn.

Rejections for Improper Form

Claims 17-29, 30, and 40-42 were objected to as being improper because a multiple dependent claim cannot depend from a multiple dependent claim. Claims 17 (from which claims 18-21 depend), 22 (from which claims 23-29 depend), 36, and 40 (from which claims 41 and 42 depend) have been amended to no longer refer to claims 1, 10-12, and 16 and to incorporate the limitations of these claims. Accordingly, this objection should be withdrawn.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-13, 15, and 16 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the disclosure in applicants' specification (1) fails to provide a written description of the claimed invention and (2) is not commensurate in scope with the claimed invention. For the following reasons, each of these rejections is respectfully traversed.

Written Description

Claims 1, 2, 4-13, 15, and 16 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the specification provides only a sequence for the *Arabidopsis NPR1* gene and therefore does not provide an adequate written description of the invention, as currently claimed. In rejecting the claims, the Examiner, in essence, asserts that (1) the "ankyrin motif is not a structural motif

unique to the claimed genus of sequences involved in disease resistance," and (2) a "representative number of species of the claimed genus" has not been described. As support for this rejection, the Federal Circuit's opinion in *Univ. of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1387 (Fed. Cir. 1997) was cited.

Applicants respectfully traverse this rejection as their specification satisfies the written description requirement set forth by the case law and the U.S. Patent & Trademark Office's Written Description Guidelines (the "Guidelines").

The Guidelines, under the "Genus Analysis" decision tree, states:

> What is a representative number of species depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. (Emphasis added.)

Given that applicants' specification describes the claimed class of acquired resistance genes and their shared, characteristic ankyrin repeats, this standard is satisfied. On this point, the Examiner's attention is directed to applicants' specification, for example, at page 6 (line 12) and at page 8 (line 9), where it is stated that an "acquired resistance polypeptide includes an ankyrin-repeat motif." Additionally, the specification, at page 43 (line 27) – page 44 (line 1) states:

> The cDNA sequence [NPR1] was analyzed using the BLAST sequence analysis program. This analysis revealed that the NPR1 protein shared significant homology with ankyrin, including the region identified as the ankyrin-repeat consensus.

As discussed in the attached Declaration of inventor Dr. Frederick Ausubel, the amino acids numbered 262-289 and 323-371 of the translated NPR1 protein sequence show homology to a mouse ankyrin protein and an ankyrin-repeat motif, respectively (see, for example, Figure 5 of the present application). Figure 6A of the application shows the alignment of the NPR1 amino acid sequence with mouse ankyrin 3 (ANKB), and Figure 6B shows the alignment of the ankyrin repeats in NPR1 with previously reported ankyrin repeat consensus sequences. As discussed by Dr. Ausubel, the *npr1-1* mutant in which the conserved histidine in the third ankyrin repeat consensus is replaced by a tyrosine displays susceptibility to virulence pathogens even after SAR induction (see, for example, pages 36-41 and 47 of the specification). This mutant phenotype was complemented by a comsid contig containing the NPR1 gene. In describing this mutant, Famodu *et al.* (WO 00/28036, Exhibit 2) states:

> [t]he lesion in one *npr1* mutant allele disrupted the ankyrin consensus sequence, suggesting that these repeats are important for NPR1 function. Furthermore, transformation of the cloned wild-type *npr1* gene into *npr1* mutants not only complemented the mutations, restoring the responsiveness to SAR induction with respect to PR-gene expression and resistance to infections, but also rendered the transgenic plants more resistant to infection by *P. syringae* in the absence of SAR induction (Cao et al. (1997) cell 88:57-63) (page 1, line 34 through page 1, line 2).

Thus, the ankyrin repeat disclosed in applicants' specification is an important motif for structurally defining this novel class of acquired resistance genes.

Dr. Ausubel further states that the claimed family of disease-resistance polypeptides with a role in disease resistance are readily distinguishable from

unrelated ankyrin-repeat-containing polypeptides that have been described in the literature, which, to the best of applicants' knowledge, have not been shown to possess this property. Moreover, because acquired resistance plant defense responses are ubiquitous in the plant kingdom, and because applicants have demonstrated that an ankyrin-repeat-containing polypeptide controls the onset of such responses in *Arabidopsis*, it is entirely reasonable to assume that other plants possess and express such genes to regulate disease resistance. Based on applicants' description, one skilled in the art would immediately recognize that applicants' invention encompassed — not one gene — but a family of genes encoding ankyrin-repeat-containing, disease resistance polypeptides.

In a further analysis of the written description requirement, the Guidelines provide an example (Example 17), where the specification disclosed rat cDNA sequences only, but claimed a mammalian or human cDNA sequence. The written description requirement was held not to be satisfied in this case, because:

> . . .neither the specification nor the general knowledge of those skilled in the art provide evidence of <u>any partial structure</u> which would be expected to be <u>common</u> to the members of the genus. Moreover, there is <u>post filing evidence</u> that indicates that there is a <u>lack of structural relationship</u> between the rat insulin cDNA sequences and other mammalian insulin cDNA sequences. (Emphasis added.)

Thus, the implication is that had there been at least a partial structure common to members of the genus, or post-filing evidence of a structural relationship between the members of the genus, then the written description requirement would have been satisfied. The Guidelines, citing applicable case law, also state:

> A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1998). (Emphasis added.)

The facts of this case fall squarely within the Office's Written Description Guidelines. The present specification discloses that the claimed genus includes genes encoding polypeptides having an ankyrin repeat, a structural feature common to members of the genus. As discussed by Dr. Ausubel, post-filing evidence presented by Bougri *et al.*[1] demonstrates that acquired resistance genes from wheat, corn, and rice share "significant sequence homology in the region of ankyrin repeats" with the *Arabidopsis* NPR1 acquired resistance gene, signifying that this structural feature is common to members of the genus. Thus, one skilled in the art would appreciate that other nucleic acids that hybridize to the *Arabidopsis* NPR1 gene also encode ankyrin-repeat-containing, disease resistance polypeptides.

In summary, there can be no question that applicants were in possession of the claimed genus at the time their application was filed, that this genus does indeed include a family of ankyrin repeat disease resistance proteins, and that one skilled in the art would recognize applicants' disclosure as a description of the invention defined by the present claims. As a result, applicants' specification clearly satisfies

[1] See Bougri *et al.*, Acquired Resistance Genes in Plants, WO 00/70069 (Exhibit 1), page 32 (lines 15-17) (Exhibit 1).

the written description requirement, as set forth by the case law, and applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

Scope of Enablement

Claims 1, 2, 4-13, 15, and 16 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the teaching of applicants' specification is not commensurate in scope with the present claims. The rejection essentially turns on the assertion that it would require undue trial and error experimentation to identify genes that are structurally and functionally related to the disclosed isolated nucleic acid molecules encoding the NPR1 polypeptides.

Applicants submit that, contrary to this assertion, their specification clearly enables the subject matter presently claimed simply by providing applicants' newly identified *NPR1* sequence. As stated in the Ausubel Declaration, genes falling within the scope of applicants' claims could routinely be identified and isolated from a variety of plant sources using nothing more than standard techniques of molecular biology based on the teaching of the specification and the level of skill known in the art at the time the present application was filed.

With respect to gene isolation methodologies, clear instructions for isolating other claimed nucleic acid molecules are provided in the specification under the heading "Isolation of Other Acquired Resistance Genes," at pages 50-52. As stated by Dr. Ausubel, genes falling within the claims may be readily isolated using such

techniques, absent undue experimentation, from virtually any plant using applicants' *NPR1* sequence as a starting material. On this point, the Examiner is referred to the case of *In re Wands* (858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)), which sets forth the CAFC standard for enablement in the biotechnology arts. *Wands* holds that an invention is enabled so long as the teaching of the specification provides the invention without undue experimentation. *Wands* states that:

> the test [for determining whether experimentation is undue] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (emphasis added).

Applying this standard to the present case, it is clear that applicants' specification satisfies this first test outlined by the CAFC in *Wands*. According to *Wands*, a considerable amount of experimentation is permissible, if it is merely routine. Looking to applicants' situation, any "experimentation" involved in isolating and characterizing additional nucleic acid molecules falling within the present claims is straightforward, and is rendered so by applicants' discovery of the sequence encoding NPR1. As explained by Dr. Ausubel, if one skilled in the art wished to isolate homologous NPR sequences from other plants, they would simply use applicants' disclosed nucleotide sequences as a probe in combination with conventional gene screening methods, such as hybridization. These approaches

would require only standard applications of hybridzation wash conditions, and possibly the type of empirical condition adjustments carried out routinely, and successfully, by molecular biologists in isolating a gene.

Applicants also note that as the case of *In re Wands* (858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)) makes clear, enablement is not negated by the necessity for some experimentation such as routine screening. The nature of molecular biology is that it involves screening recombinant libraries to determine which clone within a library contains the gene with the desired characteristics. Like the practitioners of the monoclonal antibody art described in *Wands*, who screened many hybridomas to isolate the one having the desired characteristics, practitioners in the art of molecular biology are prepared to screen many clones to find one that contains a desired gene. Screening of a recombinant library to isolate an NPR gene sequence falling within applicants' claims is considered to be a routine step in the process of isolating a gene having desired characteristics; it cannot constitute undue experimentation. In addition, Dr. Ausubel indicates that once isolated, these gene sequences may be subjected to standard DNA sequencing to confirm their structural relatedness to the disclosed *NPR1* gene and its encoded ankyrin-repeat-containing polypeptide.

In addition, as further evidence that genes encoding applicants' ankyrin repeat-containing, disease resistance polypeptides may be isolated using nothing more than standard techniques, applicants demonstrated the successful and

straightforward isolation of an *NPR1* homolog from tobacco (see, for example, pages 49 and 50). This homolog was identified by screening a cDNA library with a probe prepared from the full-length *Arabidopsis NPR1* cDNA. The isolated solanaceous acquired resistance gene encodes an ankyrin-containing polypeptide and has significant sequence identity to the *Arabidopsis NPR1* gene product. Consistent with these results in tobacco are the results described in the present specification at page 52 (lines 4-15). There, results of an RNA blot experiment are described that demonstrate the existence of yet another *NPR1*-hybridizing RNA, in this case, in potato.

The Ausubel Declaration states that such data strongly corroborate the assertion that structurally related gene sequences falling within applicants' claimed invention exist, and that they may be identified and isolated from a variety of plant sources using applicants' *NPR1* sequence and standard techniques that are both described in the present specification and known in the art. There can be no question that the guidelines provided by the teachings of applicants' disclosure have been effective for such gene identification from at least two plants other than *Arabidopsis*, and a plant family other than crucifers, and there is no reason to believe that *NPR1* homologs cannot similarly be identified from any number of other sources.

With respect to the further issue of whether such genes would confer disease resistance, Dr. Ausubel notes that the ability of a structurally related gene to confer

plant disease resistance is easily established using any of a variety of methods, including a straightforward, one-step screening technique (see, for example, page 69, lines 15-17). The specification makes clear that broad-spectrum pathogen resistance is readily obtained by expressing an acquired resistance transgene to initiate a plant defense response. Moreover, at pages 45-46, the specification demonstrates that overexpression of a *35S-NPR1* transgene in *Arabidopsis* conferred resistance on the plant to bacterial and fungal pathogens. Additionally, the Declaration of inventor Dr. Xinnian Dong, filed February 8, 2001, demonstrates that overexpressing *Arabidopsis* NPR1 in rice enhances disease resistance. Accordingly, a skilled worker need only prepare transgenic plants overexpressing a gene found to be structurally related to *NPR1*, and then evaluate the plant's ability to combat a pathogen. Such a single-step screening approach cannot and does not constitute undue trial and error experimentation.

Additionally, applicants note that the Examiner grounds the rejection on the assertion that there is no "definitive evidence demonstrating the existence of a structurally related DNA encoding a polypeptide comprising an ankyrin repeat motif." This assertion is incorrect. On this point, applicants again direct the Examiner's attention to Bougri's ankyrin repeat containing Npr homologs. In particular, applicants direct the Examiner's attention to Bougri, at page 52, where under the heading "Analysis of transgenic rice for enhanced resistance," Bougri

states that "[t]ransgenic overexpression of *Nph1* and *Nph2-1*[2] Npr homologs promotes strong resistance against *M. grisea*." Further confirming applicants' teaching, Bougri, at page 52 (lines 26-27), states that "these results suggest that both wheat and rice Npr homologs, when expressed in rice, enhance the SAR pathway." Thus, as discussed by Dr. Ausubel, Bourgri not only corroborates that applicants' claimed acquired resistance gene family encodes polypeptides having an ankyrin repeat, but also corroborates that such proteins, when overexpressed in rice, confer enhanced disease resistance to a plant pathogen.

Furthermore, Dr. Ausubel states that Crane *et al.* (U.S.P.N. 6,504,084, Exhibit 3) describes the isolation of the NPR gene from maize. One of the maize sequences was identified as part of the NPR gene based on its homology to the NPR1 gene. In particular, Crane states:

> [a] BLAST search of the Pioneer Hi-Bred Int'l Inc. propriety database identified a sequence, 798034, as homologous to NPR1. CJRMC70, the longest fragment was used to screen a lamda cDNA library made from 6 inch maize seedlings (genotype B73) cloned into λ Express (Stratagene; La Jolla, Calif.). (column 45, lines 48-53).

In characterizing this gene, Crane reports:

> [p]rotein sequence homology was calculated based on PILEUP alignment of derived amino acid sequences of Arabidopsis NPR1 and maize NPR1. DNA coding-region homology was estimated from an alignment of the open reading frames based on the amino acid PILEUP alignment. The cDNA alignment showed 1,677 positions aligning (not counting the gaps) with 824 positions containing the same base (49.1% identity). The alignment of the amino acid sequences derived from the cDNA sequence of Arabidopsis NPR1 and maize NPR1 shows a total of 579 positions aligning (not counting

[2] The *Nph1* and *Nph2-1* genes are described by Bougri (WO 00/70069; Exhibit 1) at page 8 (lines 15-22) as being *Npr1* homologs respectively from rice and wheat.

> gaps) and 222 positions (38.3% identity) with identical amino acids and 302 positions (52.2% similarity) with identical or similar amino acids. (column 46, lines 23-36).

Additionally, the Ausubel Declaration discusses the identification of several NPR1 genes, from corn, rice, and wheat, using the *Arabidopsis thaliana* NPR1 gene. In particular, the Examiner is again directed to Famodu, which reports that "cDNA clones encoding NPR1s were identified by conducting BLAST ... searches for similarity to sequences contained in the BLAST 'nr' database" (page 16, lines 6-9). Under the header "Characterization of cDNA Clones Encoding NPR1" Famodu further states that "[t]he BLASTX search using EST sequences from clones listed in Table 3 revealed similarity of the polypeptides encoded by the cDNAs to NPR1 from *Arabidopsis thaliana* (NCBI General Identifier No. 1773295)" (page 16, lines 25-27). Based on this analysis, Famodu concludes:

> [s]equence alignments and BLAST scores and probabilities indicate that nucleic acid fragments comprising the instant cDNA clones encode a substantial portion of one corn, two rice, and one wheat NPR1. These sequences represent the first corn, rice, and wheat sequences encoding NPR1. (page 17, lines 16-19).

Applicants note that these rice, wheat, maize, and corn Npr homologs were identified using knowledge of the Arabidopsis *NPR* gene discovered by applicants and gene isolation methods known *at the time applicants' application was filed.* The identification of these homologs did *not* involve the use of improved gene isolation methods that were developed *after the filing date of applicants' application.* Thus, the post-filing evidence of Bougri, Crane, and Famodu

corroborates applicants' assertion that the present application enables the routine identification of other Npr homologs using standard methods available *at the time the present application was filed.* In particular, the CCPA has indicated that post-filing publications may be used to determine the state of the art existing on the date an application is filed and the relative ease of practicing the invention. For example, the PTO can use later appearing art "as evidence of the state of art *existing on the filing date* of an application." *In re* Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). Additionally, post-filing date tests using material and computer programs commercially available on the filing date demonstrated the "relative ease" of developing embodiments. *See Bruning v. Hirose*, 161 F.3d 681, 48 USPQ2d 1934 (Fed. Cir. 1998).

Given this evidence of rice, wheat, maize, and corn Npr homologs, there is no scientific reason for doubting the existence of the claimed gene family of disease resistance polypeptides. This evidence also demonstrates the ability of skilled artisans to readily identify additional NPR genes based on the structural characteristics of their sequence homology to the Arabidopis NPR1 gene provided by applicants' specification and the presence of an ankyrin repeat motif.

Moreover, even if, as the Examiner suggests, not every nucleic acid falling within Applicants' claims would be successful at conferring disease resistance in a plant or plant component, this does not mean the present claims are overbroad. The Federal Circuit has long held that it is not necessary for all possible embodiments of

a claim to be operative in order for that claim to be enabled. *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 U.S.P.Q. (Fed. Cir. 1984). The proper test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). In analyzing what constitutes undue experimentation, applicants again note that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400.

At the time of filing, a skilled artisan, using no more than routine experimentation and the teachings of the present specification, could easily screen structurally related genes using standard techniques to determine the level of resistance provided by any particular ankyrin-repeat-containing polypeptide against a plant pathogen. The situation is, in all important aspects, indistinguishable from the facts in *Wands* in which the Federal Circuit held that the applicant's claim was enabled, despite the necessity for screening, because the process of screening was straightforward.

The Board of Patent Appeals and Interferences recently held a specification to be enabling for integration of a desired gene into fish embryos even though the methods described in the specification had a success rate of only 1%. *Ex Parte Chen*, 61 U.S.P.Q.2d 1025 (Bd. Pat. App. & Interf. 2000). In defending its

decision, the Board noted that "the examiner offers no evidence which would reasonably support a conclusion that one skilled in this art would regard this rate of success for integration of the rtGH gene as evidencing undue experimentation. We remind the examiner that some experimentation may be required as long as it is not undue." *Id.* The Board noted that the low success rate for integration of the gene merely demonstrated the need for a repetitive procedure, but was not sufficient to show that undue experimentation was required to practice the invention. *Id.* Since the Patent Office, in this case, has not offered any evidence that the instantly claimed invention would require undue experimentation to practice, it has not carried its burden of showing a reasonable basis to doubt the enablement of the present claims.

Applicants also point out that, to sustain an enablement rejection, the Office has the initial burden to establish a reasonable basis to question the enabling nature of an applicant's specification. Thus, in a case in which the PTO questions the enablement of a claim, the CCPA, in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367, 369 (CCPA 1971) has stated that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis added).

The MPEP (§ 2164.04, Eighth Edition, August 2001) further emphasizes the *Marzocchi* standard in stating that:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure (emphasis added).

Applicants note that for all of the aforementioned reasons no scientific evidence currently made of record in this case establishes a basis for doubting the objective truth of the statements found in applicants' specification regarding enablement with respect to isolating genes falling within applicants' claims and determining whether such genes possess disease resistance properties. As is discussed above, applicants' statement that expression of an acquired resistance gene encoding a polypeptide possessing an ankyrin repeat confers pathogen resistance on host plants is in accordance with the evidence described in the present specification for the *NPR1* gene and the post-filing evidence of Bougri. Moreover, given the evidence described above, the Examiner has provided no evidence or reason for doubting applicants' statement that other genes having the structural features described by applicants would function similarly as disease resistance genes.

In conclusion, the facts in the present case compel withdrawal of the § 112, first paragraph enablement rejection, and applicants request reconsideration on this issue.

Rejection under 35 U.S.C. § 102

Claims 1, 2, 4-13, 15, and 16 were rejected, under 35 U.S.C. § 102(e), as being anticipated by Ryals (U.S.P.N. 6,091,004). Applicants note that the Ryals reference is a U.S. patent claiming subject matter that overlaps with that claimed by the present application. Thus, the reference can only be overcome by establishing priority of invention through interference proceedings. *See* MPEP (8th ed.) § 2306 and 2308.01. Applicants believe they are the first to invent the claimed subject matter. Accordingly, this 102(e) rejection should be withdrawn, and an interference should be declared to resolve this issue.

Double Patenting

Claims 1, 2, 4-13, 15, and 16 were provisionally rejected under the judicially created doctrine of double patenting as unpatentable over claims of copending application Serial No. 09/908,323. Applicants note that they will file a necessary terminal disclaimer, if appropriate, once otherwise allowable subject matter has been determined.

Conclusion

Applicants submit that the claims are now in condition for allowance, which action is respectfully requested. If at least one of the pending claims in this application is found allowable and is claiming the same invention as at least one claim of the Ryals '004 patent, applicants respectfully request that the Examiner proceed to propose an interference. Enclosed are a Petition to extend the period for replying to the Office action for three months, to and including April 18, 2003, a check in payment of the required extension fee, and a check for the required fee for additional claims.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 18, 2003

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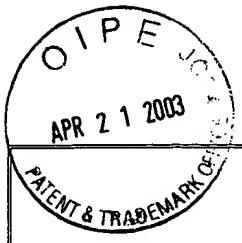

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Kristina Levites
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Xinnian Dong *et al.*	Art Unit:	1638
Serial No.:	08/908,884	Examiner:	A. Kubelik
Filed:	August 8, 1997	Customer No.:	21559
Title:	ACQUIRED RESISTANCE GENES AND USES THEREOF		

Commissioner For Patents
Washington, D.C. 20231

Version with Markings to Show Changes Made

In the specification:

A marked-up version of the title is presented below.

NUCLEIC ACIDS ENCODING A PROTEIN THAT CONFERS RESISTANCE TO A PLANT PATHOGEN AND USES THEREOF
[ACQUIRED RESISTANCE GENES AND USES THEREOF]

A marked-up version of the paragraph on page 33, line 23 through page 34, line 15 of the specification is presented below.

To carry out fine mapping of the *NPR1* gene, new CAPS and RFLP markers were generated from clones that the genetic maps in the AtDB database at Stanford's Arabidopis genome website [(http://genome-www.stanford.edu/Arabidopsis/)] showed were located between *GAP-B* and *m315*. Cosmid *g4026* (CD2-28, *Arabidopsis* Biological Resource Center, The Ohio State University, Columbus, OH) was cut with the restriction enzyme *Eco*RI and a 4-kb fragment was used to identify a polymorphism between Col-0 and La-*er* after the genomic DNA was digested with *Hind*III. Using this RFLP marker, six heterozygotes were detected among the twenty-three F3 families that were heterozygous at *GAP-B*. None were found among the seven F3 families that were heterozygous at *m315*. Therefore, g4026 is ~5.92 cm on the centromeric side of the *NPR1* gene. Cosmid *g11447* (obtained from the collection of Dr. Howard Goodman at the Massachusetts General Hospital (Nam et al., *Plant Cell* 1:699-705, 1989)) was used to generate a CAPS marker. End-sequences of an 0.8-kb *Eco*RI fragment were used to design PCR primers (primer l: 5' GTGACAGACTTGCTCCTACTG 3' (SEQ ID NO:15); primer 2: 5' CAGTGTGTATCAAAGCACCA 3' (SEQ ID NO:16) which amplified a fragment displaying a polymorphism when digested with the *Eco*RV restriction enzyme. Among the 436 *npr1-1* F3 progeny tested using this newly generated CAPS marker, seventeen heterozygotes were discovered. Since these heterozygotes were all homozygous Col-0 for the *GAP-B* locus, the *g11447* marker was placed ~1.95 cM on the telomeric side of the *NPR1* gene.

A marked-up version of the paragraph on page 35, lines 1-16, is presented below.

A partial physical map of chromosome I at University of Pennsylvania's genomics website [(http://cbil.humgen.upenn.edu/~atgc/ATGCUP.html)] showed a YAC contig that includes *m305*. The YACs in this contig, as well as left-end-fragments of YAC clones yUP19H6, yUP21A4, and yUPllH9 were obtained from Dr. Joseph Ecker at the University of Pennsylvania. The yUP19H6L end-probe was found to detect an *Rsa*I polymorphism, and five recombinants were identified among the *GAP-B* recombinants on the centromeric side of the *NPR1* gene (as shown by the vertical arrows in Fig. 1). The yUP11H9L end-probe was found to detect a *Hind*III polymorphism, and one heterozygote was found among the seventeen recombinants for *gll447* on the telomeric side of the *NPR1* gene (as shown by a vertical arrow in Fig. 1). Since yUP11H9L hybridized with the yUP19H6 YAC clone, these results showed that the *NPR1* gene is located on yUP19H6. In addition to *m305*, yUP21A4L (detects an *Eco*RI polymorphism) and *g8020* (a 1.3-kb *Eco*RI fragment that detects a *Hind*III polymorphism) were found to be very closely linked to the *NPR1* gene

with no recombinants identified. *m305*, yUP21A4L, and *g8020* all hybridized to the yUP19H6 YAC clone, further supporting the conclusion that yUP19H6 contains the *NPR1* gene.

A marked-up version of the paragraph on page 42, line 14 through page 43, line 1, is presented below.

M13-20 and M13 reverse primers were used to initiate the sequencing reactions of the *Hind*III fragments. Various restriction enzymes were then used to generate deletions in these *Hind*III subclones to analyze sequences more distal to the ends of the fragments. In addition, primers were designed to perform primer walking. The relative positions of these *Hind*III fragments were determined and gaps between these fragments were filled by sequencing analyses using *Xba*I-subclones of cosmid 21A4-P5-1 as templates. The sequence data were analyzed to identify restriction enzyme sites, to perform sequence alignment and to search for open reading frames using standard DNA analysis software (DNA Strider 1.1, MacVector 4.0.1, and GeneFinder). Using this software only one putative gene was found. Sequence data were also compared to the TIGR *Arabidopsis thaliana* DataBase using the TIGR website [(http://www.tigr.org/tdb/at/at.html)]. The results of this study identified an expression sequence tagged (EST) clone that showed homology with a portion of the 1.96-kb fragment. This portion of the 1.96-kb fragment was also identified as part of the gene recognized using GeneFinder software. The nucleotide sequence of the 7.5-kb genomic region encoding the *NPR1* gene product is shown in Fig. 4.

A marked-up version of the abstract on page 98, lines 3-5, is presented below.

Genomic and cDNA sequences, chimeric genes, vectors, cells, and plants encoding plant acquired resistance proteins, such as NPR1 from *Arabidopsis thaliana* and *Nicotiana glutinosa*, are disclosed. Expression of these polypeptides in transgenic plants is [are] useful for providing enhanced defense mechanisms to combat plant diseases. For example, the present invention provides methods for enhancing disease resistance in a plant by transforming the plant with a vector encoding an acquired resistance polypeptide with an ankyrin repeat that confers resistance to a plant pathogen.

In the claims:

A marked-up version of claims 17, 22, 36, and 40 and new claims 43-48 are presented below.

17. (Amended) A transgenic cell comprising (i) an [the] isolated nucleic acid molecule encoding an acquired resistance polypeptide comprising an ankyrin repeat, (ii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the genomic nucleic acid sequence of Fig. 4 (SEQ ID NO:1), (iii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the cDNA of Fig. 5 (SEQ ID NO:2), (iv) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the DNA sequence of Fig. 7A (SEQ ID NO:13), [of any one of claims 1 or 10-12] or (v) a [the] vector comprising said nucleic acid molecule and directing expression of the polypeptide encoded by said nucleic acid molecule [of claim 16], wherein said acquired resistance polypeptide confers, on a plant expressing said polypeptide, resistance to a plant pathogen.

22. (Amended) A transgenic plant comprising (i) an [the] isolated nucleic acid molecule encoding an acquired resistance polypeptide comprising an ankyrin repeat, (ii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the genomic nucleic acid sequence of Fig. 4 (SEQ ID NO:1), (iii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the cDNA of Fig. 5 (SEQ ID NO:2), (iv) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the DNA sequence of Fig. 7A (SEQ ID NO:13), [of any one of claims 1 or 10-12] or (v) a [the] vector comprising said nucleic acid molecule and directing expression of the polypeptide encoded by said nucleic acid molecule [of claim 16]; wherein said acquired resistance polypeptide confers, on a plant expressing said

polypeptide, resistance to a plant pathogen; and [,] wherein said nucleic acid molecule or said vector is expressed in said transgenic plant.

36. (Amended) A method of producing an acquired resistance polypeptide, said method comprising the steps of:(a) providing a cell transformed (i) an [the] isolated nucleic acid molecule encoding an acquired resistance polypeptide comprising an ankyrin repeat, (ii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the genomic nucleic acid sequence of Fig. 4 (SEQ ID NO:1), (iii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the cDNA of Fig. 5 (SEQ ID NO:2), (iv) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the DNA sequence of Fig. 7A (SEQ ID NO:13), [of any one of claims 1 or 10-12] or (v) a [the] vector comprising said nucleic acid molecule and directing expression of the polypeptide encoded by said nucleic acid molecule [of claim 16], wherein said acquired resistance polypeptide confers, on a plant expressing said polypeptide, resistance to a plant pathogen;

(b) culturing the transformed cell to express the nucleic acid molecule or the vector; and

(c) recovering the acquired resistance polypeptide.

40. (Amended) A method of providing an increased level of resistance against a disease caused by a plant pathogen in a transgenic plant, said method comprising the steps of:

(a) producing a transgenic plant cell (i) an [the] isolated nucleic acid molecule encoding an acquired resistance polypeptide comprising an ankyrin repeat, (ii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the genomic nucleic acid sequence of Fig. 4 (SEQ ID NO:1), (iii) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the cDNA of Fig. 5 (SEQ ID NO:2), (iv) an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule

comprising the DNA sequence of Fig. 7A (SEQ ID NO:13), [of any one of claims 1 or 10-12] or (v) a [the] vector comprising said nucleic acid molecule and directing expression of the polypeptide encoded by said nucleic acid molecule [of claim 16], wherein said acquired resistance polypeptide confers, on a plant expressing said polypeptide, resistance to a plant pathogen; and

(b) regenerating a transgenic plant from the plant cell wherein the nucleic acid molecule or the vector is expressed in the transgenic plant and the transgenic plant is thereby provided with an increased level of resistance against a disease caused by a plant pathogen.

43. (New) The isolated nucleic acid of claim 1, wherein said nucleic acid complements an acquired resistance mutant.

44. (New) The isolated nucleic acid of claim 43, wherein said mutant is an *Arabidopsis npr* mutant.

45. (New) The method of claim 36, wherein said wherein said nucleic acid complements an acquired resistance mutant.

46. (New) The method of claim 45, wherein said mutant is an *Arabidopsis npr* mutant.

47. (New) The method of claim 40, wherein said nucleic acid complements an acquired resistance mutant.

48. (New) The method of claim 47, wherein said mutant is an *Arabidopsis npr* mutant.